Remarks

By this amendment, claims 34-36 and 41-45 are cancelled, and claims 33, 37, 38, 39, and 40 are amended. Claim 33 has been amended to specify that the mutant herpes simplex virus is HSV1716 (a mutant of strain 17). Claims 37-40 hare been amended to change their dependency in light of the claims cancelled herein. After entry of this amendment, **claims 33 and 37-40 are pending in the application**. No new matter is added by this amendment.

Acknowledgement of Information Disclosure Statement(s)

Applicants request that the Examiner acknowledge receipt and consideration of the Information Disclosure Statement and one reference submitted to the Office on June 2, 2003, by returning a copy of the Form 1449 with the next action.

Cited References by Office

The following disclosures are cited against the invention.

1. US 6,139,834 (Martuza)
2. Markert *et al.* – *Neurosurgery* 32: 1993
3. WO92/13943 (Brown)
4. Maclean *et al.* – *J. Gen. Virol.* 72: 1991
5. US6,340,673 (Roizman)

Roizman, Martuza and Markert all worked on a mutant R3616 of HSV strain F. Although Martuza teaches the additional deletion in the ribonucleotide reductase (RR) gene, Roizman only teaches the deletion of the γ34.5 gene of HSV. However, Roizman specifically teaches that R3616 infects neuronal cells (neuroblastoma cells) and therefore may be used to bring about neuronal cell death. Indeed, Roizman teaches against the use of the mutant virus to treat non-neuronal cells (see for example Col. 18 lines 9 to 15 and Col. 20 lines 10 to 32).

Martuza (US6, 139, 834) does teach the treatment of non-neuronal cells, but with a different strain (strain F) and a different mutant (having an additional RR deletion).

MacLean *et al.* and WO 92/13943 (Brown) teach the existence of HSV1716, but there is no disclosure or suggestion in these references that this mutant could be used for the treatment of non-neuronal cancers.

Novelty

Claims 33 and 37-40 are rejected as allegedly anticipated by Martuza *et al.*, and separately as allegedly anticipated by Roizman *et al.* Applicants traverse these rejections.

None of the cited documents discloses the use of the mutant herpes simplex virus HSV1716 for the treatment of non-neuronal cancers, as now required by all of the pending claims. Accordingly, all claims as filed herewith are novel. Applicants request that the rejections under 35 U.S.C. §102 be withdrawn.

Obviousness

Claims 33 and 37-40 are rejected as allegedly obvious in light of Martuza *et al.* in combination with MacLean *et al.*, Brown *et al.*, or Markert *et al.*, and separately as allegedly obvious in light of Roizman *et al.* in combination with Martuza *et al.* and MacLean *et al.* or Brown *et al.* Applicants traverse all of these rejections.

When applying 35 U.S.C. §103, the following tenets of patent law must be adhered to:

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) Reasonable expectation of success is the standard with which obviousness is determined.

Each of these are taken in turn below.

(A) The claimed invention must be considered as a whole:

The present invention concerns the treatment of non-neuronal cancer using a very specific deposited mutant of HSV strain 17, namely HSV1716.

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination:

MacLean *et al.* and WO 92/13943 both disclose the mutant HSV1716. However, neither teach that the mutant could be used in the treatment of non-neuronal cancers. Indeed, MacLean *et al.* teach (Col. 2, p638) that the "avirulence of 1716 is due to its inability to replicate within the central nervous system". The passage goes on to say "*The candidate target cells in the central nervous system are neurons and it is supposed that the replication defect is only manifest in the central nervous system environment...*". Thus, although the mutant HSV1716 is disclosed, there is a direct teaching **against** its potential use in treating anything of a non-neuronal origin.

Roizman (US 6,340,673) teaches the use of a different mutated strain (strain F) for the treatment of neuronal cells. Although the disclosure is to a different mutant of a different strain, it could be said to support the teaching of MacLean *et al.*, and thereby teaches away from the current invention rather than rendering it obvious.

This leaves the teaching of Martuza (US 6,139,834), which discloses the use of a mutant HSV for the treatment of non-neuronal cells. However, the mutant HSV is not only a different strain (strain F) from HSV1716 (strain 17), but further is a different mutant (γ34.5 and RR gene null mutant).

Therefore, the question is whether the person of ordinary skill in the art would be motivated to combine the teaching of MacLean *et al.* and/or WO 92/13943 with that of Martuza (US 6,139,834). It is submitted that the skilled person would not make this combination for at least the following reasons.

Firstly, "the references themselves must suggest the desirability of making the combination." They do not. MacLean *et al.* describes the mutant HSV1716, but the scientific review concludes that the properties of this strain "**only manifest in the central nervous system neuronal environment**."

This means that the skilled person would have to go against the teaching of this scientific review to combine its teaching with that of Martuza.

Secondly, there is no motivation for the skilled person to choose the very specific mutant HSV1716 to combine with the teaching of Martuza. Martuza relates to not only a different strain (strain F) but a different mutant (γ34.5 and RR null mutation). Given the existence of many hundreds of thousands of HSV strains, even HSV-1 strains, and indeed the number of HSV mutant variants, there is no motivation to choose to combine the teaching of these particular strains. This combination could only be made with the use of impermissible hindsight in light of Applicants' specification. This brings us to the next point.

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention:

It is only with the benefit of hindsight that one can pick and choose features from prior art documents in order to arrive at the present invention. This is not permissible in determining whether or not an inventive step has taken place.

The invention relates to a particular mutant namely, mutant HSV1716 of HSV1 strain 17 for use in treating non-neuronal cells. The particular mutant and its properties are described, for example, in MacLean *et al.* Of the prior art documents cited, only Martuza *et al.* describes the treatment of non-neuronal cells using a mutant HSV, which, as pointed out above, describes not only a different strain of HSV but also a different mutant. The choosing of this feature (HSV1716), which goes against the teaching in the art for this particular mutant of HSV (as discussed above for MacLean *et al.*), can only have been made with the benefit of hindsight, which is impermissible.

(D) Reasonable expectation of success is the standard with which obviousness is determined:

Finally, even if assuming for the sake of argument that the person of ordinary skill would (as opposed to could) have combined the teaching of MacLean *et al.* and/or WO 92/13943 with the teaching of Martuza *et al.*, the question remains as to whether he would have done so with an

expectation of success. Applicants submit that the person of ordinary skill would not have had any expectation of success.

As mentioned above, the reference cited which describes HSV1716 does not teach that this very specific mutant virus could be used for the treatment of non-neuronal cancer. Further, a scientific review of HSV1716 (MacLean *et al.*) stated that this strain's properties "only manifest in the central nervous system neuronal environment." Thus, there was direct teaching relating to this very specific virus, stating that its relevant property (the inability to replicate) was only visible in neuronal cells.

Although the Martuza disclosure suggests that a mutant HSV can be used to treat non-neuronal cells (though none of the Martuza examples support this suggestion), this was using a mutant HSV having no relation to the very specific mutant HSV1716 now claimed. Firstly, HSV1716 is an HSV strain 17 virus, whereas Martuza uses HSV strain F; and secondly, the actual mutant used in Martuza is different in that it is a double mutant (γ34.5 and RR gene null mutant) whereas HSV1716 is just γ34.5 null.

To go against the teaching in the art, the skilled person could only have been provided with an expectation of success to combine the teaching of the two documents if there was a direct relationship between the two HSV mutants being used. This is not so. Consequently, no expectation of success existed.

Based on the foregoing arguments, and the amendments presented herewith, Applicants request that the rejections of the claims under 35 U.S.C. §103 be withdrawn.

Conclusion

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending claims in this application is believed warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

Respectfully submitted,

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